REMARKS

Claim 76 has been canceled, and Claims 70, 77, 78 and 81 have been amended, to point out with greater clarity and particularity the subject matter regarded by the Applicants as their invention. Applicants respectfully submit that the amendments to Claims 70, 77, 78 and 81 are supported throughout the Specification.

The amendment to claim 70 incorporates the substance of now cancelled Claim 76 into Claim 70. Claims 77, 78 and 81, which had formerly depended on the now cancelled Claim 76, have been amended to change their dependencies from being to cancelled Claim 76.

The amendment to Claim 70, that incorporates the substance of the now cancelled Claim 76, indicates that the cell membrane-impermeant, potent specific inhibitor of MN/CA IX used in the diagnostic/prognostic method of Claim 70 is "conjugated to a label or a visualizing means," and that "said label or said visualizing means on cells in [a vertebrate] . . . sample" is detected or detected and quantified. As a result of that amendment to Claim 70, all the pending Claims 67-70, 72-75 and 77-90 now concern methods comprising the use of a MN/CA IX-specific inhibitor which is either "conjugated to a label or a visualizing means" [Claims 67, 68, 70, 72-75, 77-82 and 86-88] or "linked to an imaging agent" [Claims 69, 83-85 and 89-90].

Applicants respectfully conclude that no new matter has been entered by any of the above amendments. As the proposed amendments only cancel a claim or present rejected claims in better form for consideration on appeal, and require only a relatively cursory review by the Examiner as they only provide greater unity to the

claimed invention, Applicants respectfully submit that the above amendments comply with the requirements of 37 CFR 1.116(b)(1)-(2), and respectfully request their entry.

I. 35 USC 112, ¶1 (Enablement) Rejection

Claims 67-70 and 72-90 stand

> rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method of diagnosing cancer and/or hypoxia in a tissue and in vivo imaging of a tumor and/or hypoxic tissue in a patient comprising administering a labeled antibody which specifically binds CA IX, wherein overexpression of CA IX is indicative of cancer, does not reasonably provide enablement for [such] a method . . . comprising administering a CA-IX specific inhibitor selected from compounds 1-91.

[Final Office Action, at page 2.] The Final Office Action concludes the lack of enablement rejection by stating: "[I]t would require undue experimentation for one of skill in the art to perform the method of the claim as written." [Final Office Action, middle of page 7.] Applicants respectfully traverse, first relying on their arguments presented in their response dated June 27, 2007, then explaining the significance of the above claim amendments in light of evidence presented, and then making a number of significant points that are briefly described immediately below and then elaborated in detail infra.

Applicants respectfully remind the Examiner that the initial burden to challenge a presumptively enabling disclosure is upon the Examiner [MPEP § 2164.04]. The Federal Circuit quoted from In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971) in In re Brana, 34 USPQ2d 1437 at 1441 (Fed. Cir. 1995) as follows:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing

> and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

[Emphasis in the original.]

Applicants respectfully submit that the Examiner has not overcome the strong presumption that the Specification as filed is enabling, having provided insufficient "reason to doubt" the truth of the statements in the Specification relied upon for enabling support. However, even if hypothetically sufficient evidence of "reason to doubt" the truth of the statements had been provided, Applicants have dispelled such a hypothetical "reason to doubt."

Applicants respectfully submit that as a result of the above amendments to the claims, all the pending Claims 67-70, 72-75 and 77-90 concern methods comprising the use of a MN/CA IX-specific inhibitor which is either "conjugated to a label or a visualizing means" [Claims 67, 68, 70, 72-75, 77-82 and 86-88] or "linked to an imaging agent" [Claims 69, 83-85 and 89-90]. Applicants respectfully submit that the evidence herein provided shows that had there ever been any reason to doubt statements in the Specification relied upon for enabling support, that such reason to doubt is certainly dispelled for at least any labeled CA IX-specific inhibitors. Evidence is provided of improved specificity and potency of labeled MN/CA IX-specific inhibitors for CA IX over other critical CA isozymes, in comparison to tests for potency and specificy for the same unlabeled MN/CA IX-specific inhibitors. That evidence confirms teachings of the Specification. That evidence essentially is from data in the three exemplary attached references -- Svastova et al., FEBS Lett., 577: 439-445 (2004), Cecchi et al., J Med.

Chem., 48: 4834-4841 (2005), and Alterio et al., J Am. Chem. Soc., 128: 8329-8335 (2006).

Based on the teachings in the instant specification, one of skill in the art would expect that a "label," "visualizing means" or "imaging agent" that is either conjugated or linked to a MN/CA IX-specific inhibitor would render said inhibitor to be even more selective for MN/CA IX than for other CA isoenzymes. Subsequent experiments have confirmed the teachings of the instant specification. Two of the attached references – Svastova et al. (2004), supra and Cecchi et al. (2005), supra – provide evidence that exemplary **labeled** MN/CA IX-specific inhibitors are more potent against CA IX than the unlabeled MN/CA IX-specific inhibitors, and more selective for CA IX as compared with other CA isozymes.

A further highly significant point is that MN/*CA9* is known to be one of the most (if not the most) tightly regulated by hypoxia of all genes tested for such regulation. [See, for example, Wykoff et al., Cancer Res., 60: 7075-7083 (2001).] CA IX is the only CA isoenzyme that is tightly regulated by tumor hypoxia. Evidence provided herein shows that exemplary **labeled** MN/CA IX-specific inhibitors have been recently **visually** shown to bind **only** to overexpressed, membrane-bound CA IX that is **activated by hypoxia** and not to any other CAs, whether intracellular or on the cell surface, nor to CA IX overexpressed under normoxia. Labeled exemplary MN/CA IX-specific inhibitors have been shown to accumulate specifically only in hypoxic tumors overexpressing CA IX and not in normal tissues. The attached reference of Alterio et al. (2006), supra shows that at least one exemplary MN/CA IX-specific inhibitor is currently in clinical studies as an imaging tool for acute hypoxic tumors.

Applicants also make the point that an inhibitor's membrane-impermeability automatically separates its binding from the intracellular (cytosolic and mitochondrial) CA isoenzymes (CA I, CA II, CA V and CA VII) and only allows the inhibitor to bind potentially to the membrane-associated CA isoenzymes (CA IV, CA IX, CA XII and CA XIV). Exemplary MN/CA IX-specific inhibitors, such as, fluorescein-labeled aromatic sulfonamides, have been shown to be membrane-impermeant, and would then necessarily favor CA IX over any of the intracellular CA isozymes.

Applicants will discuss each of the above points in more detail below. In view of CA IX being the only CA to be regulated by hypoxia, and that MN/CA IX-specific inhibitors bind selectively to hypoxically activated CA IX, and that labeled inhibitors were expected to bind more selectively to CA IX than to other CAs because of CA IX's larger active site (as disclosed in the Specification), and to have enhanced potency, and that evidence is provided that supports those points made in the Specification, Applicants respectfully conclude that a very compelling case has been made that there is no reason to doubt statements in the Specification relied upon for enabling support for the claimed methods.

A. Teaching in the Specification: Labeled Sulfonamides Expected to Favor CA IX

Based on the teachings in the instant specification, one of skill in the art would expect that a "label," "visualizing means" or "imaging agent" that is either conjugated or linked to a MN/CA IX-specific inhibitor would render said inhibitor to be even more selective for MN/CA IX rather than for other CA isoenzymes. The Specification teaches that MN/CA IX's active site is larger than any of the other widely

distributed relevant carbonic anhydrase isoenzymes, such as CA I, CA II and CA IV. [See, for example, the Specification at least at page 9, lines 1-4; at page 50, lines 3-5; and at page 54, lines 6-8]. As the "label," "visualizing means," or "imaging agent" conjugated/linked to a MN/CA IX-specific inhibitor would render the inhibitor bulkier, one of skill in the art would expect that that bulkier compound would fit into the larger sized active site of MN/CA IX before it would fit into the smaller sized active sites of other CA IX isoenzymes, where it would have difficulty in fitting or be barred from fitting.

Such label-related increased selectivity of MN/CA IX-specific inhibitors is shown by a comparison of the results of screening assays for Compound 5 (homosulfanilamide) of the instant invention when it is unconjugated and then when it is conjugated to a label. Compound 5 is shown in Table 1 of the Specification (page 60, line 15) to have greater specificity towards MN/CA IX then to CA I, CA II and CA IV, but with a K_I of 103 nM (the preliminary screening result reported in Table 1), the unconjugated Compound 5 would not be considered to be a potent inhibitor of MN/CA IX in accordance with the pending claims, wherein such potency is established as "to be less than about 50 nanomolar. . . ." However, the accompanying reference, Svastova et al. (2004), supra, shows that Compound 5 (homosulfanilamide) when conjugated to FITC [CAI #3 in Svastova et al.] has a K_I value against CA IX of **24 nM** [Svastova et al. (2004), at page 440, top of col. 2], that is, the labeled Compound 5 is a potent inhibitor of MN/CA IX.

Specification Refers to Experiments Reported in Svastova et al. (2004)

As reported in Svastova et al. (2004), FITC-homosulfanilamide, an exemplary MN/CA IX-specific inhibitor conjugated to a label, is used to visualize CA IX on the surface of MDCK cells under conditions of hypoxia but not under normoxia after 48 hours incubation [Svastova et al. (2004); Figure 2(C), at page 441]. MN/*CA9* is known to be one of the most (if not the most) tightly regulated by hypoxia of all genes tested for such regulation. [See, for example, Wykoff et al. (2000), supra.] The selectivity of FITC-homosulfanilamide (an exemplary MN/CA IX-specific inhibitor conjugated to a label) for hypoxically-induced CA IX is additional evidence that supports that the claimed methods are adequately enabled.

Page 27, lines 1-6 of the Specification refers to experiments wherein FITC-labeled sulfonamides are

> labeled exemplary CA IX-specific inhibitors, such as labeled sulfonamides, for example, conjugated to fluorescein isothiocyanate (FITC), are shown to bind to the surface of MN/CA IX transfected cells, and not to control cells, only in hypoxia but not in normoxia. Those experiments confirm that CA IX-specific inhibitors, such as the sulfonamide compounds described herein, can specifically target MN/CA IX under conditions characteristic of intratumoral microenvironments.

[Emphasis added.] In that quote, "[t]hose experiments" are referring to the experiments of Svastova et al. (2004) (accompanying article). Applicants respectfully point out that the experiments of Svastova et al. (2004) support the diagnostic/prognostic use of CA IX inhibitors conjugated to labels such as FITC, as well as the improved specificity for CA IX of a labeled MN/CA IX-specific inhibitor over the unlabeled MN/CA IX-specific

inhibitor. Such exemplary in vitro experiments also support the instant claims directed to in vivo imaging [Claims 69, 83-85 and 89-90].

In view of that Svastova et al. (2004) example, and disclosure in the Specification that the active site of CA IX is larger than that of other CAs tested, one of skill in the art would expect that a MN/CA IX-specific inhibitor conjugated to a "label," "visualizing means" or "imaging" agent would be more selective for CA IX than the unconjugated inhibitor and more selective towards CA IX than other CA isozymes.

B. Cecchi 2005: Fluorescent Sulfonamides Have Improved Selectivity for CA IX over Other CAs

Cecchi et al. (2005), supra (copy attached) provides evidence that representative labeled MN/CA IX-specific inhibitors of the instant invention show improved affinity for CA IX and improved specificity for CA IX over all physiologically relevant CA isozymes, in comparison to the same representative unlabeled inhibitors. Those representative MN/CA IX inhibitors are Compounds 2, 3, 5-10, 15 and 16, which correspond to the FITC-conjugated Compounds 5h, 5a, 5b-5g, 5j and 5i, respectively, of Cecchi et al. (2005). As expected in view of the above-referenced teachings of the Specification, the FITC-conjugated MN/CA IX-specific inhibitor Compounds 2, 3, 5-10, 15 and 16 showed improved affinity for CA IX and improved specificity for CA IX over the other critical CA isozymes tested, than the unconjugated to FITC (that is, unlabeled) Compounds 2, 3, 5-10, 15 and 16 did in accordance with the preliminary screening reported in the instant Specification. That comparison of the inhibition constants (K_Is) of the unlabeled versus the FITC-labeled Compounds 2, 3, 5-10, 15 and 16 of the Specification, identified in Cecchi as compounds **5h, 5a, 5b, 5c, 5d, 5e, 5f, 5g, 5j,** and

5i (respectively) are shown in the table of **APPENDIX I** (attached hereto at pages 31-32).

For example, FITC-labeled Compound 5, which in Svastova et al. (2004) was already shown to have improved specificity for CA IX [K_I of 24nM versus 103nM for unlabeled Compound 5], was shown in Cecchi et al. (2005) to favor CA IX over CA I and CA II [K_Is of 1450nM and 44nM, respectively.] In fact, for every inhibitor tested in Cecchi et al. (2005), the FITC-labeled compound exhibited 1) greater affinity for CA IX [had a lower K_I], and 2) higher affinity for CA IX than for any of the other CAs tested (CA I and CA II), as compared with the unlabeled compound. In addition to having improved specificity via their affinity for CA IX, the FITC-labeled compounds are likely to be membrane-impermeant, as FITC-labeled Compounds 5 and 6 of the instant specification were shown to be in Cecchi et al. (2005) (Compounds **5b** and **5c**, discussed infra), and therefore to be doubly specific for CA IX.

Those results of Cecchi et al. (2005) also support the imaging use of the CA IX inhibitors conjugated to labels such as FITC, as claimed in the methods of the invention.

C. Alterio et al. (2006): Exemplary FITC-CA IX Sulfonamide in Advanced Clinical Imaging Trials

As further evidence of the enablement of the claimed methods, Applicants respectfully point out that clinical imaging trials have begun with the FITC-labeled conjugate of Compound 6 [reported in Alterio et al., J Am Chem Soc., 128(25):8329-8335 (2006); copy attached]. FITC-labeled Compound 6 of the instant specification is identified as "Compound **1**" in Alterio et al. (2006). Alterio et al. (2006) states that the

compound "is in clinical studies as an imaging tool for acute hypoxic tumors . . ." [Abstract], and refers to the compound as "in advanced clinical studies for its use as a diagnostic tool for the imaging and/or treatment of hypoxic tumors, which are nonresponsive to classical chemo- and radiotherapy." [Alterio et al. (2006); top of col. 1, page 8330.]

The Abstract also refers to differences in the binding of that compound to CA II compared with models of binding to CA IX, which **"may account for the roughly 2 times higher affinity of 1** [that compound which is Compound 6 of the instant invention] **for hCA IX over hCA II and may explain why in vivo the compound specifically accumulates only in hypoxic tumors overexpressing CA IX and not in the normal tissues."** [Emphasis added. Applicants respectfully point out that that compound, Compound 6 of Appendix I, shows a K_I of 24nM against CA IX, and a K_I of 45nM against CA II.] Applicants submit that Alterio et al. (2006) is strong evidence that preferential CA IX inhibition provides sufficient enablement for the claimed methods, as clinical imaging trials have begun with at least one of the exemplary labeled MN/CA IX-specific inhibitors of the instant invention that exhibits preferential CA IX inhibition.

Applicants respectfully conclude that the improved selectivity and potency of labeled MN/CA IX-specific inhibitors of the invention over the unlabeled inhibitors, and against the other critical CA isozymes, as taught by the instant specification and as evidenced by Svastova et al. (2004), Cecchi et al. (2005) and Alterio et al. (2006), strongly supports that the presumptively enabling Specification is enabling for the claimed methods.

Applicants respectfully respond below to individual additional arguments presented by the Examiner in the Final Office Action.

II. Examiner's Additional Arguments

1. No Working Examples

At the top of page 10 of the Office Action, the Examiner reiterates his previous assertion that the Specification apparently provides no working examples for an in vivo method of imaging and diagnosis:

> [T]he Examiner recognizes that although Applicants contemplate and claim an in vivo method of imaging and diagnosis, the specification appears to be silent on any working examples. Moreover, the specification has not taught the amount of necessary for successful diagnosis or imaging, the number of times the inhibitor needs to be administered or the most appropriate route of administration.

Applicants first respectfully point out that at the time of filing an application, an applicant need not have any examples, relying on arguments previously presented in the response dated June 27, 2007, particularly at pages 23-36. Applicants further respectfully argue that the experiments referred to in the above-cited passage at page 27, lines 1-6 of the Specification, and later published in Svastova et al. (2004) constitute a working example, i.e., experiments wherein

> labeled exemplary CA IX-specific inhibitors, such as labeled sulfonamides, for example, conjugated to fluorescein isothiocyanate (FITC), are shown to bind to the surface of MN/CA IX transfected cells, and not to control cells, only in hypoxia but not in normoxia. Those experiments confirm that CA IX-specific inhibitors, such as the sulfonamide compounds described herein, can specifically target MN/CA IX under conditions characteristic of intratumoral microenvironments.

[Emphasis added.]

Applicants also respectfully point to the guidance regarding administration of the CA IX-specific inhibitors provided in the Specification at page 11, lines 7-21:

> The CA IX-specific inhibitors of this invention can be administered in a therapeutically effective amount, preferably dispersed in a physiologically acceptable nontoxic liquid vehicle. Different routes of administration may be preferred depending on the site or type of preneoplastic/neoplastic disease, for example, solid or non-solid tumor or metastasis. In general, parenteral administration would be preferred to avoid undesired effects of systemic treatment, for example, those that could be occasioned by binding of the inhibitors to the gastrointestinal mucosa. Injection into or into the vicinity of the preneoplastic/neoplastic disease would be generally preferred. . . . The pharmaceutical formulation would be designed in accordance with known standards as suitable for the route of administration.

[Emphasis added.]

Applicants respectfully point out that "a specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art." [In re Myers, 161 USPQ 668, 671 (CCPA 1969); see also, G.E. Col. v. Brenner, 159 USPQ 335 (CAFC 1968).] As the Federal Circuit stated in Spectra-Physics, Inc. v. Coherent, Inc., 3 USPQ2d 1737, 1743 (Fed. Cir. 1987): "A patent need not teach, and preferably omits, what is well known in the art." [Emphasis added.]

Further, it would be routine experimentation to determine which dosage and what route(s) of administration would be preferred. Methods have long been established for determining the dosage and routes of administration for drug sulfonamides such as acetazolamide, methazolamide, etc. As advanced clinical trials for one of the exemplary MN/CA IX-specific inhibitors began last year [Alterio et al.

(2006)], Applicants respectfully conclude that such determinations would not require undue experimentation

2. Supuran and Scozzafava 2000: Preferential Inhibition of CA IX "Insufficient"

In response to Applicants' previous amendments and arguments in their response dated June 27, 2007, that the CA IX-specific inhibitors need only be shown to be potent and preferential CA IX inhibitors for the claimed methods to be sufficiently enabled, the Examiner reiterates his previous arguments that Supuran et al. [Supuran and Scozzafava, Exp. Opin. Ther. Patents 2000, 10(5): 575-600] teach that CA isozymes show high or very high and similar affinities for sulfonamide inhibitors (Final Office Action, at page 9), and although some of the 91 sulfonamide inhibitors had nanomolar affinity towards CA IX, "many of these 'CA IX specific' inhibitors also have similar affinities and in some instances higher affinities for other CA isozymes. For example, the Specification teaches that compounds 14-21 all had nanomolar affinities for CA IX, as well as for CA II, below 50 nanomolar." [Final Office Action, passage bridging pages 9 and 10].

Also, at the bottom of page 9, the Examiner contends that "in view of the teachings of Supuran et al., one of ordinary skill in the art would recognize that a more than preferential affinity for CA IX would be needed to practice the claimed invention." [Emphasis added.] Applicants respectfully point out that those statements of Supuran and Scozzafava (2000) were made before the analysis of the CA IX's active site disclosed in the instant invention, and the discovery that the CA IX active site is larger than those of the other physiologically relevant CA isozymes. The Examiner has not

addressed or considered the effect of the larger size of the labeled sulfonamide inhibitors (which would favor the CA IX active site; discussed supra), let alone their potential membrane impermeance or their affinity for the only CA isozyme activated by hypoxia.

As stated at page 592 (top col. 2) in the cited Supuran and Scozzafava (2000) article:

> Some progress in this field [of CA isozyme specific inhibition] has been recently registered, by the development of low molecular weight membrane-impermeant inhibitors [Scozzafava et al., J Med Chem, 43: 292-300 (2000)] which, being excluded from the intracellular space, inhibit selectively only CA IV and not the cytosolic CA I and CA II.

Because only CA IX and not CA IV is overexpressed in cancer, a membrane-impermeant inhibitor that inhibits CA IX with a K_I in nanomolar levels should be useful for imaging CA IX, regardless of the inhibitor's affinity for CA I, CA II or any other CA isozymes found intracellularly, even if those intracellular CA isozymes have nanomolar or similar affinities. "Since CA IX is one of the few extracellular carbonic anhydrases, a membrane-impermeant selective inhibitor of CA IX would be doubly selective for this enzyme and thereby avoid side effects associated with nonspecific CA inhibition." [Specification at page 8, lines 10-12.] Applicants respectfully point out that the inhibition constants shown in Tables 1-3 of the instant specification (comparing inhibition of CA I, CA II, CA IV and CA IX by the representative inhibitors) were determined by in vitro screening without the normal physical barriers of cell membranes.

The Specification teaches that positively charged CA IX-specific inhibitors, such as, for example, labeled derivatives of the disclosed pyridinium derivatives of sulfonamides (i.e., Compounds 27-91) of the instant invention, would be expected to be

membrane-impermeant. [Specification at the least at page 7, lines 16-22; at page 52, line 31 to page 53, line 22; at page 62, lines 25-33; at page 65, lines 10-21.] Table 4 of the instant specification (at page 60) shows that all of the four pyridinium sulfonamides tested (Compounds 71, 76, 89 and 91) were membrane-impermeant: "Different cationic sulfonamides synthesized by us here, such as **71, 76, 89, 91, . . .**, were detected only in very small amounts within the blood red cells, proving that they were unable to penetrate through the membranes, obviously due to their cationic nature," [Specification, at page 53, lines 11-14; emphasis added.]

The Specification summarizes the significance of membrane-impermeance of the disclosed compounds at page 62, lines 28-33:

> Since these compounds are membrane-impermeant due to their salt-like character, and as hCA IX is present on the extracellular side of many tumors with poor clinical prognosis, compounds of this type target specifically this tumor-associated CA isozyme without affecting the cytosolic CAs known to play important physiological functions. Thus, compounds of this type may constitute the basis of new anticancer therapies based on CA inhibitors.

Secondly, as taught in the instant specification, other unique characteristics of CA IX favor its detection by the CA IX-specific inhibitors of the invention under preneoplastic/neoplastic conditions:

> CA IX was found by the inventors also to contribute to acidification of extracellular pH in hypoxia but not in normoxia *(unpublished data)*. The latter result indicates that hypoxia up-regulates both expression level and enzyme activity of CA IX, that is, hypoxia activates the CA catalytic activity of CA IX. That is a very important finding because intratumoral hypoxia is a clinically relevant factor increasing aggressiveness of tumor cells and reducing success of therapy. Hypoxia is usually accompanied by acidification of extracellular microenvironment, which facilitates tumor invasion and metastasis.

[Specification at page 9, lines 10-17.] That is, the increased extracellular acidification of hypoxic tumors (beyond increased lactic acid levels) which favors tumor growth has primarily been associated with hypoxically-induced CA IX among the extracellular CAs; the above-cited passage from the instant specification enhances that association, as hypoxia both induces and activates CA IX.

Further evidence has since been provided in Robertson et al. [Cancer Research, 64: 6160-6165 (2004); copy enclosed], wherein experiments using *CA9*-specific RNAi demonstrated that all of the increase in CA activity under hypoxia is caused by CA IX as opposed to any other membrane-bound CA. That increased enzymatic activity of CA IX under hypoxia (i.e., altered conformation) can translate into increased affinity for the labeled CA IX-specific inhibitors of the invention:

> Further, **labeled exemplary CA IX-specific inhibitors,** such as labeled sulfonamides, for example, conjugated to fluorescein isothiocyanate (FITC), are **shown to bind to the surface of MN/CA IX transfected cells, and not to control cells, only in hypoxia but not in normoxia. Those experiments confirm that CA IX-specific inhibitors,** such as the sulfonamide compounds described herein, **can specifically target MN/CA IX under conditions characteristic of intratumoral microenvironments.**

[Specification, at page 27, lines 1-6; emphasis added.]

Further evidence is provided by Svastova et al. (2004) and Cecchi et al. (2005) [copies attached]. For example, the FITC-labeled Compound 5 of the instant specification was shown in Cecchi et al. (2005) ("Compound **5b**") to have a K_I of 44nM against CA II, and a K_I of 26nM against CA IX. The same compound was also demonstrated in Cecchi et al. (2005) to be essentially membrane-impermeant (Table 2). Therefore, it is not surprising that the same compound was shown in Figure 2(C) of

Svastova et al. (2004) ("Compound **CAI #3**") to only bind hypoxic cells that overexpress activated CA IX, as also supported by experiments measuring extracellular pH changes under normoxia and hypoxia [Svastova et al. (2004); Figure 2(B)].

Similarly, the FITC-labeled Compound 6 of the instant specification was found in Cecchi et al. (2005) ["Compound **5c**"] to have a K_I against CA II of 45nM, and a K_I against CA IX of 24nM and also to be membrane-impermeant (Table 2). Again, as demonstrated visually in Cecchi et al. (2005), Figure 1(b), the FITC-labeled Compound 6B ["compound 5c" in Cecchi et al. (2005)] only bound cells overexpressing CA IX, only under conditions of hypoxia.

Finally, the initiation of advanced clinical imaging trials as reported in Alterio et al. (2006) indicates that CA IX preferential inhibition using the disclosed labeled inhibitors, represented by the exemplary FITC-Compound 6, provides strong evidence that the labeled CA IX-specific inhibitors used in the claimed methods have the requisite specificity for CA IX and selectivity for CA IX over other physiologically relevant CA isozymes.

4. Parkkila et al. 1995 and Parkkila et al. 2000

At page 10 of the Final Office Action, the Examiner states: "Applicants appear to have taken the teachings of Parkkila et al. [Parkkila et al., PNAS, 97: 2220-2224 (2000); Parkkila et al., Histochemical J., 27: 974-982 (1995)] out of context because these references were cited to show that other CA isozymes are found in malignant tissues, as well as normal tissues; and not intended to compare the other isozymes directly with CA IX." Applicants respectfully acknowledge Examiner's

argument, but submit that the teachings of the Specification, that preferential CA IX inhibition by the labeled inhibitors of the methods of this invention can be sufficient for tumor imaging purposes, are confirmed by the experiments of Svastova et al. (2004) and Cecchi et al. (2005) as disclosed at length above.

Conclusion

Applicants respectfully conclude that the above remarks and described evidence rebut any possible burden that could have been shifted to the Applicants by the Examiner's challenges to the Specification's "presumptively enabling disclosure." Applicants respectfully remind the Examiner that MPEP § 2164.04 entitled "Burden on the Examiner Under the Enablement Requirement" directs that the initial burden of proof to challenge a presumptively enabling disclosure is upon the Examiner. The patent case law, as well as the MPEP, makes clear that in accordance with case law, statements in a patent specification relied upon for enabling support that correspond in scope to a claimed invention "*must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of" those statements. [In re Marzocchi, 169 USPQ 367, 369 (CCPA 1971); italicized emphasis in the original; underlined emphasis added.]

Applicants respectfully conclude that insufficient evidence of "reason to doubt" the objective truth of statements relied upon for enabling support in the Specification for the claimed invention has been provided to carry the initial burden of proof. However, Applicants respectfully further conclude that even if that hypothetical

initial burden had been shifted to the Applicants, that the Applicants would have dispelled that hypothetical burden by the above explanations, remarks and evidence.

Applicants finally conclude that the pending claims, particularly in view of the above amendments, have the sufficient support required for enablement, and respectfully request that the Examiner withdraw the instant 35 USC 112, first paragraph rejection.

III. Nonstatutory Double Patenting Rejection

Claims 74-75 stand

> provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4, 9-10, 12-18 and 31-32 of copending Application No. 11/222,986. Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus.

[Office Action, at page 11.] Applicants respectfully submit that as the instant application and U. S. Patent Application No. 11/222,986 are commonly owned, that the enclosed terminal disclaimer over U.S. Patent Application No. 11/222,986 obviates the subject nonstatutory obviousness-type rejection of Claims 74-75.

The Office Action states at page 11:

> A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

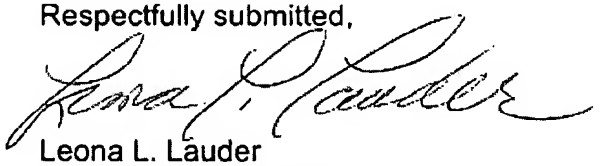
The undersigned Attorney for the Applicants declares that the cited U.S. Patent Application No. 11/222,986 and the instant application are commonly owned. A terminal disclaimer over U.S. Patent Application No. 11/222,986 and the required terminal disclaimer fee payment are enclosed.

Applicants respectfully conclude that the subject nonstatutory obviousness-type double patenting rejection is obviated by the enclosed terminal disclaimer, and respectfully request that the Examiner withdraw the subject obviousness-type double patenting rejection.

CONCLUSION

Applicants respectfully conclude that the claims as amended are in condition for allowance, and earnestly request that the claim amendments be entered, and that the claims be promptly allowed. If for any reason the Examiner feels that a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to telephone the undersigned Attorney for Applicants at (415) 981-2034.

Respectfully submitted,



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Dated: November 7, 2007

APPENDIX I
K_Is of Sulfonamide CA IX-Inhibitors:
Unlabeled ['795 Specification] versus Labeled [Cecchi 2005]

US '795 Compound #	**K_I [nM]** unlabeled	**K_I [nM]** FITC-labeled
2	CA I: 25000 CA II: 240 CA IX: 238	**"5h"** CA I: 1400 CA II: 52 CA IX: 34
3	CA I: 28000 CA II: 300 CA IX: 294	**"5a"** CA I: 1500 CA II: 41 CA IX: 29
5	CA I: 25000 CA II: 170 CA IX: 103	**"5b"** CA I: 1450 CA II: 44 CA IX: 26
6	CA I: 21000 CA II: 160 CA IX: 33	**"5c"** CA I: 1300 CA II: 45 CA IX: 24
7	CA I: 8300 CA II: 60 CA IX: 245	**"5d"** CA I: 980 CA II: 47 CA IX: 30
8	CA I: 9800 CA II: 110 CA IX: 264	**"5e"** CA I: 950 CA II: 52 CA IX: 32
9	CA I: 6500 CA II: 40 CA IX: 269	**"5f"** CA I: 1100 CA II: 43 CA IX: 35

[continued...]

US'795 Compound #	K_I [nM] unlabeled	K_I[nM] FITC-labeled
10	CA I: 6000 CA II: 70 CA IX: 285	**"5g"** CA I: 1070 CA II: 40 CA IX: 31
15	CA I: 6 CA II: 2 CA IX: 38	**"5j"** CA I: 480 CA II: 27 CA IX: 16
16	CA I: 164 CA II: 46 CA IX: 34	**"5i"** CA I: 630 CA II: 34 CA IX: 20